LABELING

DERMAGRAFT® Human Fibroblast-Derived Dermal Substitute
Essential Prescribing Information

Numbers in parentheses ( ) refer to sections in the main part of the product labeling

Device Description
DERMAGRAFT® is a cryopreserved human fibroblast-derived dermal substitute. (1)

Intended Use / Indications
(2) DERMAGRAFT is indicated for use in the treatment of wounds resulting from Dystrophic Epidermolysis Bullosa (DEB)

Contraindications
- DERMAGRAFT is contraindicated for use in wounds that have signs of clinical infection.
- DERMAGRAFT is contraindicated in patients with known hypersensitivity to bovine products, as it may contain trace amounts of bovine proteins from the manufacturing medium and storage solution. (3)

Warnings
None. (4)

Precautions
Caution: Do not use any topical agents, cytotoxic cleansing solutions, or medications (e.g., lotions, ointments, creams, or gels) on an ulcer being treated with DERMAGRAFT as such preparations may cause reduced viability of DERMAGRAFT.

Caution: Do not reuse, refreeze, or sterilize the product or its container.

Caution: Do not use the product if there is evidence of container damage or if the date and time stamped on the shipping box has expired.

Caution: Do not use DERMAGRAFT after the expiration date.

Caution: The product must remain frozen at -75°C ± 10°C continuously until ready for use.

Caution: DERMAGRAFT is packaged with a saline-based cryoprotectant that contains 10% DMSO (Dimethylsulfoxide) and bovine serum. Skin and eye contact with this packaging solution should be avoided.

Caution: Always thaw and rinse product according to the Preparation for Use instructions to ensure the delivery of metabolically active, living cells to the patient's wound.

Caution: To ensure the delivery of metabolically active, living cells to the patient's wound do not hold DERMAGRAFT at room temperature for more than 30 minutes. After 30 minutes, the product should be discarded and a new piece thawed and prepared consistent with Preparation for Use instructions. (5)

Adverse Events
(6)

Maintaining Device Effectiveness
DERMAGRAFT must be stored continuously at -75°C ± 10°C. DERMAGRAFT must be thawed and rinsed according to the Preparation for Use instructions. After the initial application of DERMAGRAFT, subsequent sharp debridement of the ulcer should continue as necessary. Additional wound preparation should minimize disruption or removal of previously implanted DERMAGRAFT. (13)

Patient Counseling Information
After implantation of DERMAGRAFT, patients should be instructed not to disturb the wound site for approximately 72 hours (three days). After this time period, the patient, or caregiver, should perform the first dressing change. The frequency of additional dressing changes should be determined by the treating physician. Patients should be given detailed instructions on proper wound care so they can manage dressing changes between visits. Patients should be advised that they are expected to return for follow-up treatments on a routine basis, until the wound heals or until they are discharged from treatment. Patients should be instructed to contact their physician, if at any time they experience pain or discomfort at the ulcer site or if they notice redness, swelling, or discharge around/from the ulcer. (8)

How Supplied
DERMAGRAFT is supplied frozen in a clear bag containing one piece of approximately 2 in x 3 in (5 cm x 7.5 cm) for a single-use application. The clear bag is enclosed in a foil pouch and labeled unit carton.

Caution: DERMAGRAFT is limited to single use application. Do not reuse, refreeze, or sterilize the product or its container.

DERMAGRAFT is manufactured using sterile components and is grown under aseptic conditions. Prior to release for use, each lot of DERMAGRAFT must pass USP Sterility (14-day), endotoxin, and mycoplasma tests. In addition, each lot meets release specifications for collagen content, DNA, and cell viability.

DERMAGRAFT is packaged with a saline-based cryoprotectant. This solution is supplemented with 10% DMSO (Dimethylsulfoxide) and bovine serum to facilitate long-term frozen storage of the product. Refer to the step-wise thawing and rinsing procedures to ensure delivery of a metabolically active product to the wound bed. (9)

Customer Assistance
For product orders, technical support, product questions, reimbursement information or to report any adverse reactions or complications, please call the following number which is operative 24 hours a day:
Smith & Nephew, Inc.
Wound Management Division
Customer Care Center
800-876-1261

Distributed By
Smith & Nephew, Inc.
Wound Management Division
11775 Starkey Road
P.O. Box 1970
Largo, FL 33779-1970

Manufactured By
Smith & Nephew Wound Management (La Jolla)
10933 North Torrey Pines Road, Suite 200
La Jolla, CA 92037-1005

Caution: Federal (U.S.) law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).

US PAT Nos. 4,963,489; 5,266,480; 5,443,950
EPC No. 0309456

DERMAGRAFT is a registered trademark of Smith & Nephew
11068/001 09/01

DERMAGRAFT®
Instructions for Use

HUMANITARIAN USE DEVICE: Federal (USA) law restricts this device to sale, distribution and use by or on the order of a physician (or a properly licensed practitioner). The effectiveness of this device for this use has not been demonstrated.

1. INDICATIONS FOR USE

Dermagraft is indicated for the treatment of wounds associated with Dystrophic Epidermolysis Bullosa (DEB).

CAUTION: This device should be used only by physicians (and properly licensed practitioners) trained in the surgical management of DEB patients, trained or experienced in the use of this device and prepared to provide patient monitoring.

2. PRODUCT DESCRIPTION

DERMAGRAFT® is a cryopreserved human fibroblast-derived dermal substitute; it is composed of fibroblasts, extracellular matrix, and a bioabsorbable scaffold. DERMAGRAFT is manufactured from human fibroblast cells derived from newborn foreskin tissue. During the manufacturing process, the human fibroblasts are seeded onto a bioabsorbable polyglactin mesh scaffold. The fibroblasts proliferate to fill the interstices of this scaffold and secrete human dermal collagen, matrix proteins, growth factors and cytokines, to create a three-dimensional human dermal substitute containing metabolically active, living cells. DERMAGRAFT does not contain macrophages, lymphocytes, blood vessels, or hair follicles.

The human fibroblast cells are from a qualified cell bank, which has been extensively tested for animal viruses, retroviruses, cell morphology, karyology, isoenzymes, and tumorigenicity. Reagents used in the manufacture of DERMAGRAFT are tested and found free from viruses, retroviruses, endotoxins, and mycoplasma before use. DERMAGRAFT is manufactured with sterile components under aseptic conditions within the final package. Prior to release for use, each lot of DERMAGRAFT must pass USP Sterility (14-day), endotoxin, and mycoplasma tests. In addition, each lot meets release specifications for collagen content, DNA, and cell viability. Maternal blood sera are tested for evidence of infection with human immunodeficiency virus type 1 (HIV-1), human immunodeficiency virus type 2 (HIV-2), hepatitis B virus, (HBV), hepatitis C virus (HCV), syphilis, human T-lymphotropic virus type 1 (HTLV-1), and found negative for the purposes of donor selection. During subsequent screening of the fibroblast cell strain at various stages in the manufacturing process, testing for these same viruses, as well as Epstein-Barr virus (EBV) and human T-lymphotropic virus type 2 (HTLV-2), is carried out and found to be negative.

DERMAGRAFT is supplied frozen in a clear bag containing one piece measuring approximately 2 in x 3 in (5 cm x 7.5 cm) for a single-use application.

3. CONTRAINDICATIONS

- DERMAGRAFT is contraindicated for use in wounds that have signs of clinical infection.
- DERMAGRAFT is contraindicated in patients with known hypersensitivity to bovine products, as it may contain trace amounts of bovine proteins from the manufacturing medium and storage solution.

4. WARNINGS

None.

5. PRECAUTIONS

Caution: Do not use any topical agents, cytotoxic cleansing solutions, or medications (e.g., lotions, ointments, creams, or gels) on an ulcer being treated with DERMAGRAFT as such preparations may cause reduced viability of DERMAGRAFT.

Caution: Do not reuse, refreeze, or sterilize the product or its container.

Caution: Do not use the product if there is evidence of container damage or if the date and time stamped on the shipping box has expired.

Caution: Do not use DERMAGRAFT after the expiration date.

Caution: The product must remain frozen at -75°C ± 10°C continuously until ready for use.

Caution: DERMAGRAFT is packaged with a saline-based cryoprotectant that contains 10% DMSO (Dimethylsulfoxide) and bovine serum. Skin and eye contact with this packaging solution should be avoided.

Caution: Always thaw and rinse product according to the Preparation For Use instructions to ensure the delivery of metabolically active, living cells to the patient's wound.

Caution: To ensure the delivery of metabolically active, living cells to the patient's wound do not hold DERMAGRAFT at room temperature for more than 30 minutes. After 30 minutes, the product should be discarded and a new piece thawed and prepared consistent with Preparation for Use instructions.

Caution: The persistence of DERMAGRAFT in the wound and the long-term safety of this device in epidermolysis bullosa has not been established. The longest course of therapy reported for this indication was 25 months, and involved 9 separate device applications with a total of 21 pieces of DERMAGRAFT applied. In vivo and in vitro testing has not revealed a tumorigenic potential for dermal fibroblast cells contained in the device. However, the long-term clinical response to these cells in unknown.

Caution: The maximum number of DERMAGRAFT applications reported in an EB patient was 32 devices applied over a 4-month period.

6. ADVERSE EVENTS

A. Epidermolysis Bullosa

In the series of patients treated for this indication, there was a reported adverse event involving a moderate staphylococcus aureus infection in one patient. This was on the right shin occurring on the date of device application, and was treated and resolved with the use of antibiotics. Infection was a recurring event with this patient but it did not appear to hinder the take of DERMAGRAFT applied to other areas. There were no serious adverse events or deaths reported.

B. All DERMAGRAFT Treated Patients

A total of 695 patients were evaluated in four clinical trials for diabetic foot ulcers; 389 treated with DERMAGRAFT, and 306 treated with Control (standard therapy). In these four clinical studies, the most common adverse event reported in patients receiving DERMAGRAFT was infection of the study wound. In the pivotal (Phase III) study for diabetic foot ulcers, 17 of 163 patients (10.4%) in the DERMAGRAFT group, and 27 of 151 patients (17.9%) in the Control group had study wound infections. In the earlier three clinical studies, 63 of 226 patients (27.9%) in the DERMAGRAFT groups, and 43 of 155 patients (27.7%) in the Control groups had study wound infections.

7. CLINICAL INVESTIGATIONS

Chronic Wounds in Patients with EB

DERMAGRAFT was used in the management of persistent erosions of six patients with dystrophic epidermolysis bullosa. A total of 34 different body sites were treated. Each patient received between 3 and 20 applications of DERMAGRAFT applied to between 3 and 12 sites. Epidermal coverage was reported as ranging between 75 and 100% after 8 weeks of treatment.

Immune Response

The potential for DERMAGRAFT to elicit an immune response was evaluated by examining the baseline and terminal sera of patients enrolled in a clinical trial of the product for the treatment of chronic foot ulcers in patients with diabetes. Using the Western Blot technique, a comparison of pre- and post-immune patient sera did not indicate an immunologic response to DERMAGRAFT in patients treated with up to 8 pieces of DERMAGRAFT.

8. HOW SUPPLIED

A. Package Description

DERMAGRAFT is supplied frozen in a clear bag containing one piece dermal replacement measuring approximately 2 in x 3 in (5 cm x 7.5 cm) for a single-use application. The clear bag is enclosed in a foil pouch and labeled unit carton.

Caution: DERMAGRAFT is limited to single use application. Do not reuse, refreeze, or sterilize the product or its container.

DERMAGRAFT is manufactured using sterile components and is grown under aseptic conditions. Prior to release for use, each lot of DERMAGRAFT must pass USP Sterility (14-day), endotoxin, and mycoplasma tests. In addition, each lot meets release specifications for collagen content, DNA, and cell viability.

DERMAGRAFT is packaged with a saline-based cryoprotectant. This solution is supplemented with 10% DMSO (Dimethylsulfoxide) and bovine serum to facilitate long-term frozen storage of the product. Refer to the step-wise thawing and rinsing procedures to ensure delivery of a metabolically active product to the wound bed.

B. Storage

DERMAGRAFT must be stored continuously at -75°C ± 10°C.

C. Shelf Life

The DERMAGRAFT unit carton is marked with the expiration date of the product. Do not use the product after this date.

9. DIRECTIONS FOR USE

A. Application Notes

Open wounds associated with Epidermolysis Bullosa must receive adequate debridement. Surgical debridement is generally reserved for the gentle removal of non-viable tissue. Autolytic products should be restricted to calcium alginates and hydrogels and the trauma associated with the use of adhesive products and from most forms of mechanical debridement must be avoided. The resulting wound bed should meet the clinical criteria for skin grafting prior to the use of DERMAGRAFT (i.e., clean, granulating wound bed)

Based on the six case studies, three to twenty pieces of DERMAGRAFT were used for treatment, depending on the size of the wound. The frequency of application ranged from 1

week to several months. The decision of how many pieces to use and the frequency of application was based on clinical judgement.

B. Materials Required for Preparation and Application of DERMAGRAFT

- Water bath/thawing tub (37°C) with lid
- Thermometer
- Sterilized scissors
- Surgical gloves
- Clock or timer
- Sterile normal saline (0.9% sodium chloride) at room temperature
- Permanent ink marker
- Sterilized blunt-end forceps
- DERMAGRAFT rinsing stand
- Dressing supplies

C. Preparation For Use

Caution: Do not use DERMAGRAFT after the expiration date.

Caution: Follow all instructions to ensure delivery of metabolically active, living cells to the patient's wound.

Caution: Do not use the product if there is evidence of container damage or if the time on the shipping box has expired.

Caution: Product must remain frozen at -75°C ± 10°C until ready to thaw. Do not reuse, refreeze, or sterilize this product or its container.

1. For each DERMAGRAFT bag, prepare a 2-Liter water bath or thawing tub containing 2 Liters of water at 34°C to 37°C. Water temperature must not exceed 37°C.

Note: The transfer of DERMAGRAFT from freezer or original shipping container into the 34°C to 37°C water bath must take no longer than 60 seconds to ensure delivery of living cells to the patient's wound.

Note: Do not thaw two pieces of DERMAGRAFT in the same water bath at the same time.

2. Remove the DERMAGRAFT box from either the freezer or the shipping box per the Storage and Transfer Instructions found in the shipping box. Close the freezer door or the shipping box, and then immediately begin the thawing process, as detailed below.

3. Tear the cardboard box open along perforation.

4. Remove the foil pouch from the box.

5. Tear open the foil pouch with your hands at the tear notch.

Note: Do not cut foil pouch with scissors.

6. Remove the clear bag containing DERMAGRAFT. Do not open the clear bag.

Note: During the thawing and rinsing steps, touch the outer margins of the bag only and avoid touching the areas of the bag that come in contact with DERMAGRAFT.

7. Within 60 seconds of removal from the freezer or original shipping container, completely submerge the clear bag in the 34°C to 37°C water. Place the thawing tub lid on the tub during the thawing process to keep the DERMAGRAFT submerged. Water temperature does not need to be monitored from this point. Allow approximately two (2) minutes for thawing. The process is complete when there are no visible ice crystals within the clear bag.

Note: Do not thaw longer than three (3) minutes to ensure delivery of living cells to the patient's wound.

8. Promptly remove the thawing tub lid and remove the clear bag from the water.

9. Handling by the clear bag's outer margins, place the bag into the rinsing stand without touching the areas of the bag that come in contact with DERMAGRAFT.

Note: A thin layer of cells in addition to the DERMAGRAFT may be present inside the clear bag. This is a normal result of the manufacturing process.

10. Secure the clear bag inside the rinsing stand by using the locking clip at the bottom of the stand. Leave the bag in this locked position throughout the rinsing procedure. Immediately begin the rinsing process (Steps 11-14).

Note: Steps 11-14 should be carried out promptly and without interruption to ensure delivery of living cells to the patient's wound.

11. Put on surgical gloves and cut the clear bag open above the cut line with sterilized scissors.

Caution: DERMAGRAFT is packaged with a saline-based cryoprotectant that contains 10% DMSO (Dimethylsulfoxide) and bovine serum. Skin and eye contact with this packaging solution should be avoided.

12. Gently squeeze the solid plastic bar to open the clear bag. Pour the liquid out. Fill the bag up to the plastic bar with room temperature sterile normal saline. Wait for five (5) seconds and then pour out the saline.

13. Refill the clear bag to the bar a second time with room temperature sterile normal saline. Wait for 5 seconds and then pour out the saline.

14. Refill the clear bag to the bar again with room temperature sterile normal saline. Wait for 5 seconds and then pour out the saline. The product has now been rinsed 3 times.

15. Fill the clear bag a fourth time with sterile normal saline and hold. If you are immediately ready to implant the product, hold the product in the saline for a minimum of 5 seconds

and then proceed to Step 16. If the patient is not ready or you need to transport the product to the patient, then cap the rinsing stand. DERMAGRAFT may be held in saline up to 30 minutes.

Note: Do not hold DERMAGRAFT at room temperature for more than 30 minutes to ensure delivery of living cells to the patient's wound. After 30 minutes, the product should be discarded and a new piece thawed and prepared consistent with Preparation For Use instructions.

Note: Dispose of all liquid, rinsing solutions, and unused pieces of DERMAGRAFT in accordance with institution or government environmental regulations.

D. Application

Caution: Do not use any topical agents, cytotoxic cleansing solutions, or medications (e.g., lotions, ointments, creams, or gels) on a wound being treated with DERMAGRAFT as such preparations may cause reduced viability of DERMAGRAFT.

16. When ready for application, completely drain the clear bag of liquid. Then release the locking clip and remove the bag from the rinsing stand.

17. Holding the clear bag by the outer margins, use a permanent marker to trace an area up to 1 cm greater than the wound size, at the physician's discretion, onto the bag either directly or from a separate tracing of the ulcer.

18. Using sterilized scissors, cut the DERMAGRAFT from the edge of the clear bag along the traced lines making allowance by creating a handling tab to facilitate the implantation of DERMAGRAFT.

19. Carefully peel the plastic from both sides of the DERMAGRAFT using sterilized forceps.

20. Implant the DERMAGRAFT into the debrided wound, covering the surface of the wound to just below the epithelial layer. With sterilized scissors trim the excess handling tab.

21. Cover the wound with a non-adherent dressing. Fill, but do not pack the wound with a dressing that provides a moist wound environment.

22. Between routine applications of DERMAGRAFT, it is important to maintain a moist wound environment.

23. After the initial application of DERMAGRAFT, subsequent sharp debridement of the wound should continue as necessary. Subsequent wound preparation should minimize disruption or removal of previously implanted DERMAGRAFT.

24. Following each application of DERMAGRAFT, the first wound dressing change should take place in approximately 72 hours.

Note: If a dressing change is needed prior to 72 hours, the non-adherent dressing layer should be left in place.

10. PATIENT INFORMATION

Patients and parents should be counseled regarding basic information about the condition, basic information about DERMAGRAFT, and how the product is used in wounds associated with recessive Epidermolysis Bullosa and post-operative care.

After implantation of DERMAGRAFT, patients should be instructed not to disturb the wound site for 72 hours (three days). After this time period, the patient or caregiver should perform the first dressing change. The frequency of additional dressing changes should be determined by the treating physician. Patients should be given detailed instructions on proper wound care so they can manage dressing changes between visits. Patients should be advised that they are expected to return to follow-up treatments on a routine basis until the wounds heal or until they are discharged from treatment. Patients should be instructed to contact their physician if at any time they experience pain or discomfort at the wound site or if they notice redness, swelling or discharge around/from the wound.

11. PEEL-OFF LABEL

Two peel-off labels are provided on the DERMAGRAFT box. One of the peel-off labels should be removed and placed on the patient's chart. This label bears a unique lot number and expiration date that will facilitate the collection of product monitoring information.

12. CUSTOMER ASSISTANCE

For product orders, technical support, product questions, reimbursement information or to report any adverse reactions or complications, please call the following number which is operative 24 hours a day:

Smith & Nephew, Inc.
Wound Management Division
Customer Care Center
800-876-1261

Manufactured By

Smith & Nephew Wound Management (La Jolla)
10933 North Torrey Pines Road, Suite 200
La Jolla, CA 92037-1005

Distributed By

Smith & Nephew, Inc.
Wound Management Division
11775 Starkey Road
P.O. Box 1970
Largo, FL 33779-1970

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